IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No. 1122
Ian David Manger et al.	Examiner: Hyun, Paul Sang Hwa
Application No.: 10/602,489	Technology Center/Art Unit: 1772
Filed: June 23, 2003	APPELLANTS' BRIEF UNDER 37 CFR §41.37
For: RECIRCULATING FLUIDIC NETWORK AND METHODS FOR USING THE SAME	

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Commissioner:

Further to the Notice of Appeal mailed on August 15, 2011 and the Notice of Panel Decision from Pre-Appeal Brief mailed on September 9, 2011 for the above-referenced application, Appellants submit this Brief on Appeal.

TABLE OF CONTENTS

1. REAL PARTY IN INTEREST

The real party in interest is Fluidigm Corporation.

2. RELATED APPEALS AND INTERFERENCES

None.

3. STATUS OF CLAIMS

Claims 14-15, 18-20, 23-31, 34-37, and 39-40 are pending in the present application. Claims 1-13, 16-17, 21-22, 32-33, and 38 are canceled. Claims 14-15, 18-20, 23-31, 34-37, and 39-40 are being appealed.

4. STATUS OF AMENDMENTS

No amendments were filed subsequent to the Final Office Action mailed on April 15, 2011.

5. SUMMARY OF CLAIMED SUBJECT MATTER

The claims of the present invention are directed to a variety of micro-fluidic devices and methods for conducting assays and syntheses. The devices include a solid substrate layer having a surface that is capable of attaching ligand and/or anti-ligand, and an elastomeric layer attached to the surface. Some embodiments have deflectable membrane valves and pumps associated therewith.

Specifically, independent claim 14 recites a method of conducting a binding assay. (*see*, e.g., page 1, paragraph [0007] or page 2, paragraphs [0015] – [0019]). The method comprises:

(a) providing a microfluidic device comprising a solid substrate layer having a surface that is capable of attaching ligand and/or anti-ligand, and an elastomeric layer attached to said solid substrate surface (*see*, e.g., page 1, paragraph [0007]), wherein said elastomeric layer comprises:

(i) a plurality of first flow channels (*see*, e.g., page 1, paragraph [0008]);

(ii) a plurality of second flow channels each intersecting and crossing each of the first flow channels thereby providing a plurality of intersecting areas formed at intersections between the first flow channels and the second flow channels, wherein the plurality of first flow channels and the plurality of second flow channels are adapted to allow the flow of a solution

therethrough, wherein the solid substrate surface is in fluid communication with at least the intersecting areas of the plurality of first flow channels and the plurality of second flow channels, and wherein the plurality of first flow channels and/or the plurality of second flow channels are capable of forming a plurality of closed looped flow channels, (*see*, e.g., page 1, paragraph [0009]) wherein the plurality of second flow channels are in communication with a pump (*see*, e.g., page 2, paragraph [0014]), and wherein a sample solution is transported through the plurality of second flow channels under the action of the pump (*see*, e.g., page 2, paragraph [0144]), wherein the pump comprises more than one control channel each formed within the elastomeric layer and separated from the plurality of second flow channels by an elastomeric segment that is deflectable into the plurality of second flow channels in response to an actuation force, whereby the sample solution is transported along the plurality of second flow channels upon independent, sequential actuation of the more than one control channels (*see* e.g., page 1, paragraph [0011], FIGS. 3A, 3B, and 7A; *see also* peristalitic pumping on page 10, paragraphs [0122] – [0124]);

(iii) a plurality of control channels (*see*, e.g., page 1, paragraph [0010]);

(iv) a plurality of first control valves each operatively disposed with respect to each of the first flow channels to regulate flow of the solution through the first flow channels, wherein each of the first control valves comprises a first control channel and an elastomeric segment that is deflectable into or retractable from the first flow channel upon which the first control valve operates in response to an actuation force applied to the first control channel, the elastomeric segment when positioned in the first flow channel restricting solution flow therethrough (*see*, e.g., page 1, paragraph [0011]);

(v) a plurality of second control valves each operatively disposed with respect to each of the second flow channels to regulate flow of the solution through the second flow channels, wherein each of the second control valves comprises a second control channel and an elastomeric segment that is deflectable into or retractable from the second flow channel upon which the second control valve operates in response to an actuation force applied to the second control channel, the elastomeric segment when positioned in the second flow channel restricting solution flow therethrough (*see*, e.g., page 2, paragraph [0012]);

(vi) a plurality of sets of closed loop forming control valves each set having a first valve operatively disposed with respect to an inlet of one of each of the first and/or the second flow channels and a second valve operatively disposed with respect to an outlet of one of each of

the first and/or second flow channels to form the plurality of closed looped flow channels (*see* FIG. 7A elements 732 and 724A and 724B), wherein each of the loop forming control valves comprises a loop forming control channel and an elastomeric segment that is deflectable into or retractable from the first and/or the second flow channels upon which the loop forming control valve operates in response to an actuation force applied to the loop forming control channel, the elastomeric segment when positioned in the first and/or the second flow channels restricting solution flow therethrough thereby forming the looped flow channel (*see*, e.g., page 2, paragraph [0013]), wherein the first valve of the set of loop forming control valves comprises a control channel of the pump that is independently actuated with respect to other control channels of the pump (*see* page 12 paragraph [0146], referring to control valves 724A and 724B; *see also* FIG. 7A); and

(vii) a plurality of recirculating pumps, and wherein each recirculating pump is operatively disposed with respect to one of the closed looped flow channels such that circulation of solution through each of the closed looped flow channels can be regulated by one of the recirculating pumps (*see*, e.g., page 2, paragraph [0014]; *see also* page 12 paragraph [0146], referring to control valves recirculating pump 728 ; *see also* FIG. 7A);

(b) applying an actuating force to the second control valves to restrict solution flow through each of the second flow channels (*see*, e.g., page 2, paragraph [0016]);

(c) introducing a reagent comprising a ligand into at least one of the first flow channels under conditions sufficient to attach the ligand to the solid substrate surface (*see*, e.g., page 2, paragraph [0017]);

(d) removing the actuation force to the second flow channel control channel and applying an actuation force to the first control channel such that solution flow through the first flow channel is restricted (*see*, e.g., page 2, paragraph [0018]); and

(e) performing a binding assay by introducing the sample solution into the second flow channel (*see*, e.g., page 2, paragraph [0019]);

(f) applying an actuating force from two control lines to the plurality of sets of closed loop forming control valves to form the plurality of closed looped flow channels such that each closed looped flow channel comprises a closed loop spanning multiple rows and multiple columns (*see*, e.g., page 12, paragraphs [0142] – [0143]), *see also* FIG. 7B depicting multiple rows and columns 704 A-H and $720A_{11}$-G_{19}); and recirculating the sample solution within the closed loop each of the closed looped flow channels using the recirculating pump under

conditions sufficient to specifically bind an anti-ligand that may be present in the sample solution to the ligand that is attached to the solid substrate surface (*see*, e.g., page 2, paragraph [0017]); and

(g) detecting the binding of the anti-ligand in the sample to the ligand (*see*, e.g., page 14, paragraph [0179]).

Claims 15, 18-20, and 23-31 are dependent claims which depend from claim 14. Claim 15 recites that the method of claim 14 further comprising removing any ligand that is not attached to the solid substrate surface from the first flow channel prior to introducing the sample solution into the second flow channel. (*see*, e.g., page 6, paragraph [0072]) Claim 18 recites that in the method of claim 14, the plurality of first flow channels and the plurality of second flow channels are located within the elastomeric layer (*see*, e.g., page 6, paragraph [0067]), and wherein each of the intersecting areas formed at intersections between the first flow channels and the second flow channels comprises a via which is in fluid communication with the solid substrate surface thereby forming a well that is adapted to collect a fluid therein. (*see*, e.g., page 2, paragraph [0022]; and page 12, paragraph [0146]). Claim 19 recites that in the method of claim 14, the first flow channel is in communication with a pump, and wherein the reagent is transported through the first flow channel under the action of the pump. (*see*, e.g., page 12, paragraph [0147]). Claim 20 recites that in claim 19, the pump comprises more than one control channels each formed within the elastomeric layer and separated from the first flow channel by an elastomeric segment that is deflectable into the first flow channel in response to an actuation force, whereby the reagent is transported along the first flow channel. (*see*, e.g., page 9, paragraph [0109]). Claim 23 recites that in claim 14, said step (e) of performing binding assay comprises removing the elastomeric layer from the solid substrate surface and determining ligand/antiligand binding at each of the intersecting areas with a detector. (*see*, e.g., page 15, paragraph [0181]). Claim 24 recites that in claim 23, the detector detects an optical signal within the intersecting areas. (*see*, e.g., page 14, paragraph [0175]; *also see* claim 24 as filed in the original Specification. Please note that this claim element would enable one of ordinary skill in the art pursuant to MPEP 2164 and 2163.06). Claim 25 recites that in claim 24, the detector detects a fluorescence emission, fluorescence polarization or fluorescence resonance energy transfer. (*see*, e.g., page 14, paragraph [0175]). Claim 26 recites that in claim 24, the detector is an optical microscope, a confocal microscope or a laser scanning confocal microscope. (*see*,

e.g., and claim 26 as filed in the original Specification. Please note that this claim element would enable one of ordinary skill in the art pursuant to MPEP 2164 and 2163.06). Claim 27 recites that in claim 23, the detector is a non-optical sensor selected from the group consisting of a radioactivity sensor, and an electrical potential difference sensor. (*see*, e.g., and claim 27 as filed in the original Specification. Please note that this claim element would enable one of ordinary skill in the art pursuant to MPEP 2164 and 2163.06). Claim 28 recites that in claim 14, the assay comprises detecting binding between a substrate and a cell receptor; a substrate and an enzyme; an antibody and an antigen; a nucleic acid and a nucleic acid binding protein; a protein and a protein; a small molecule and a protein; a small molecule and an oligonucleotide; or a protein affinity tag and a metal ion. (*see*, e.g., page 3, paragraph [0045]). Claim 29 recites that in claim 14, the assay is an assay for detecting a toxic effect on cells or a cell death assay, or a cell proliferation assay. (*see*, e.g., page 14, paragraph [0175]). Claim 30 recites that in claim 14, the assay is an oligonucleotide binding assay or a peptide binding assay. (*see*, e.g., page 3, paragraphs [0045] – [0046]). Claim 31 recites that in claim 14, the assay is an antimicrobial assay. (*see*, e.g., page 16, paragraphs [0201] – [0202]).

Independent claim 34 recites a method of conducting a binding assay. (*see*, e.g., page 1, paragraph [0007] or page 2, paragraphs [0015] – [0019]). The method comprises:

(a) providing a microfluidic device comprising a solid substrate layer having a surface that is capable of attaching ligand and/or anti-ligand, and an elastomeric layer attached to said solid substrate surface (*see*, e.g., page 1, paragraph [0007]), wherein said elastomeric layer comprises:

(i) a first flow channel; (*see*, e.g., page 1, paragraph [0008])

(ii) a second flow channel intersecting and crossing the first flow channel thereby providing an intersecting area formed at an intersection between the first flow channel and the second flow channel, wherein the first flow channel and the second flow channel are adapted to allow the flow of a solution therethrough, wherein the solid substrate surface is in fluid communication with at least the intersecting area of the first flow channel and the second flow channel, and wherein the first flow channel and/or the second flow channel are capable of forming a closed looped flow channel (*see*, e.g., page 1, paragraph [0009]), wherein the second flow channel is in communication with a pump (*see*, e.g., page 2, paragraph [0014]), and wherein a sample solution is transported through the second flow channel under the action of the pump, (*see*, e.g., page 2, paragraph [0144]) wherein the pump comprises more than one control channel

each formed within the elastomeric layer and separated from the second flow channel by an elastomeric segment that is deflectable into the second flow channel in response to an actuation force, whereby the sample solution is transported along the second flow channel upon independent, sequential actuation of the more than one control channels; (*see* e.g., page 1, paragraph [0011], FIGS. 3A, 3B, and 7A; *see also* peristaltic pumping on page 10, paragraphs [0122] – [0124])

(iii) a plurality of control channels; (*see*, e.g., page 1, paragraph [0010])

(iv) a first control valve operatively disposed with respect to the first flow channel to regulate flow of the solution through the first flow channel, wherein the first control valve comprises a first control channel and an elastomeric segment that is deflectable into or retractable from the first flow channel upon which the first control valve operates in response to an actuation force applied to the first control channel, the elastomeric segment when positioned in the first flow channel restricting solution flow therethrough; (*see*, e.g., page 1, paragraph [0011])

(v) a second control valve operatively disposed with respect to the second flow channel to regulate flow of the solution through the second flow channel, wherein the second control valve comprises a second control channel and an elastomeric segment that is deflectable into or retractable from the second flow channel upon which the second control valve operates in response to an actuation force applied to the second control channel, the elastomeric segment when positioned in the second flow channel restricting solution flow therethrough; (*see*, e.g., page 2, paragraph [0012])

(vi) a first loop forming control valve operatively disposed with respect to an inlet of one of the first and/or the second flow channels and a second loop forming control valve operatively disposed with respect to an outlet of one of the first and/or second flow channels to form the closed looped flow channel (*see* FIG. 7A elements 732 and 724A and 724B), wherein each of the first and second loop forming control valves comprises a loop forming control channel and an elastomeric segment that is deflectable into or retractable from the first and/or the second flow channels upon which the loop forming control valve operates in response to an actuation force applied to the loop forming control channel, the elastomeric segment when positioned in the first and/or the second flow channels restricting solution flow therethrough thereby forming the closed looped flow channel (*see*, e.g., page 2, paragraph [0013]), wherein the first loop forming control valve comprises a control channel of the pump that is

independently actuated with respect to other control channels of the pump (*see* page 12 paragraph [0146], referring to control valves 724A and 724B; *see also* FIG. 7A); and

(vii) a recirculating pump operatively disposed with respect to the closed looped flow channel such that circulation of solution through the closed looped flow channel can be regulated by the recirculating pump (*see*, e.g., page 2, paragraph [0014]; *see also* page 12 paragraph [0146], referring to control valves recirculating pump 728 ; *and see* FIG. 7A);

(b) applying an actuating force to the second control valve to restrict solution flow through the second flow channel (*see*, e.g., page 2, paragraph [0016]);

(c) introducing a reagent comprising a ligand into the first flow channel under conditions sufficient to attach the ligand to the solid substrate surface (*see*, e.g., page 2, paragraph [0017]);

(d) removing the actuation force to the second flow channel control channel and applying an actuation force to the first control channel such that solution flow through the first flow channel is restricted (*see*, e.g., page 2, paragraph [0018]); and

(e) performing a binding assay by introducing a sample solution into the second flow channel (*see*, e.g., page 2, paragraph [0019]);

(f) applying an actuating force to the first loop forming control valve using a first control line and to the second loop forming control valve using a second control line to form the closed looped flow channel such that the closed looped flow channel comprises a closed loop (*see*, e.g., page 12, paragraphs [0142] – [0143]); and recirculating the sample solution within the closed loop of the closed looped flow channel using the recirculating pump under conditions sufficient to specifically bind an anti-ligand that may be present in the sample solution to the ligand that is attached to the solid substrate surface (*see*, e.g., page 2, paragraph [0017]); and

(g) detecting the binding of the anti-ligand in the sample to the ligand (*see*, e.g., page 14, paragraph [0179]).

Claims 35-37 and 39-40 are dependent claims which depend from claim 34. Claim 35 recites that in claim 34, the first flow channel and the second flow channel are located within the elastomeric layer (*see*, e.g., page 6, paragraph [0067]), and wherein the intersecting area formed at the intersection between the first flow channel and the second flow channel comprises a via which is in fluid communication with the solid substrate surface thereby forming a well that is adapted to collect a fluid therein. (*see*, e.g., page 2, paragraph [0022]). Claim 36 recites that in claim 34, said step (e) of performing binding assay comprises removing the

elastomeric layer from the solid substrate surface and determining ligand/antiligand binding at the intersecting area with a detector (*see*, e.g., page 15, paragraph [0181]), wherein the detector detects an optical signal within the intersecting areas, and wherein the detector detects a fluorescence emission, fluorescence polarization, or fluorescence resonance energy transfer. (*see*, e.g., page 14, paragraph [0175]; *see also* claim 24 as filed in the original Specification. Please note that this claim element would enable one of ordinary skill in the art pursuant to MPEP 2164 and 2163.06). Claim 37 recites that in claim 34, said step (e) of performing binding assay comprises removing the elastomeric layer from the solid substrate surface and determining ligand/antiligand binding at the intersecting area with a detector (*see*, e.g., page 15, paragraph [0181]), wherein the detector detects an optical signal within the intersecting areas, and wherein the detector is an optical microscope, a confocal microscope, or a laser scanning confocal microscope (*see*, e.g., page 14, paragraph [0175]; *see also* claim 24 as filed in the original Specification. Please note that this claim element would enable one of ordinary skill in the art pursuant to MPEP 2164 and 2163.06). Claim 39 recites that in claim 34, the second flow channel is in communication with a pump comprising a plurality of sequentially actuated control channels (*see* e.g., page 1, paragraph [0011], FIGS. 3A, 3B, and 7A; *see also* peristaltic pumping on page 10, paragraphs [0122] – [0124]), and wherein the sample solution is transported through the second flow channel under the action of the pump (*see*, e.g., page 2, paragraph [0144]). Claim 40 recites that in claim 39, the first loop forming control valve comprises a control channel of the pump (*see* page 12 paragraph [0146], referring to control valves 724A and 724B; *see also* FIG. 7A).

6. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The grounds of rejection to be reviewed on appeal are:

1) Whether claims 14, 15, 18-20, 23-26, 28-31, 34-37, 39, and 40 are obvious under 35 U.S.C. § 103(a) over Van Dam et al. (U.S. Pub. No. 2003/0008411) in view of Quake et al. (U.S. Pub. No. 2002/0037499); and

2) Whether claim 27 is obvious under 35 U.S.C. § 103(a) over Van Dam et al. in view of Quake et al. and further in view of Raillard et al. (U.S. Pub. No. 2002/0102577).

7. ARGUMENT

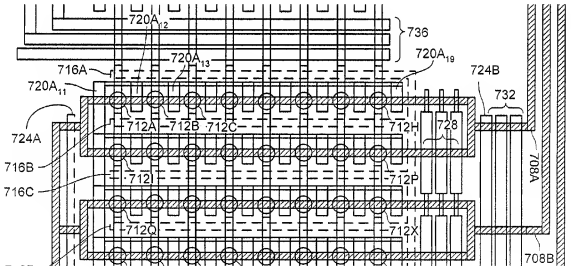
Claims 14-15, 18-20, 23-26, 28-31, 34-37, and 39-40

In the Final Office Action dated April 15, 2011, claims 14-15, 18-20, 23-26, 28-31, 34-37, and 39-40 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Van Dam et al. (U.S. Patent Application Publication No. 2003/0008411) in view of Quake et al. (U.S. Patent Application Publication No. 2002/0037499). The Appellants respectfully traverse.

1) The cited references, either alone, or in combination, do not teach or suggest that the first valve of the set of loop forming control valves comprises a control channel of the pump.

Claim 14 is drawn to a method of conducting a binding assay and FIG. 7A, a portion of which is reproduced below, illustrates an embodiment of the present invention. The method includes, among other steps, transporting a sample solution through flow channels using a pump (e.g., pump 732 in FIG. 7A). Once the sample solution is present in the flow channels, one of the control channels of the pump (e.g., valve 724B) and a second valve (e.g., valve 724A) are used to form one of a plurality of closed loops. The sample solution is then recirculated within the closed loop using a recirculating pump (e.g., recirculating pump 728). It should be noted that the pump used to transport sample solution to the flow channels (e.g., pump 732) is ***outside*** the closed loop. The recirculating pump (e.g., recirculating pump 728) is ***inside*** the closed loop, as appropriate for recirculating fluid once the closed loop is formed.

FIG. 7A



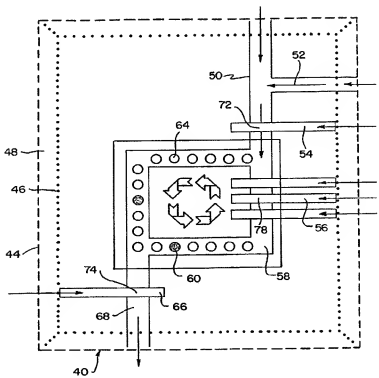
Claim 14 recites a particular implementation in which "the first valve of the set of loop forming control valves [e.g., valve 724B] comprises a control channel of the pump [the third (i.e., left-most) control channel of pump 732]," among other elements. Thus, valve 724B serves a dual function as both a first valve of the set of loop forming control valves (724B &

724A) as well as a control channel of pump 732. The use of one of the control channels of the external pump as a valve to form a closed loop is not taught or suggested by either Van Dam or Quake.

In the Final Office Action, the Examiner admits that Van Dam does not disclose the step of manipulating the valves to form a closed loop as recited in claim 14 and attempts to use Quake to make up for this deficiency in Van Dam. Quake does discuss (in relation to FIG. 14) a mixing and/or detection loop actuated by a peristaltic pump formed of microvalves. However, Quake fails to teach or suggest a loop forming control valve that is a control channel of an external pump as recited in claim 14.

MPEP 2413.03 requires that "[A]ll words in a claim must be considered in judging the patentability of that claim against the prior art." In the Final Office Action, the Examiner makes conclusory statements that Quake teaches the claim elements addressed above, despite the fact that Quake fails to teach or suggest these claim elements and thereby fails to comply with MPEP 2413.03.

FIG. 14



As illustrated in FIG. 14 of Quake (reproduced above), microvalve 72 is used to open and close the sample inlet channel 50 and microvalve 74 is used to open and close the

sample outlet channel 68, thereby forming target loop 58. Sequential operation of valves 78 is used to create a peristaltic pumping action as illustrated by the counterclockwise arrows.

Quake transports the sample to closed loop 58 using a pump that is outside the outer dashed lines and not shown in FIG. 14. Quake provides no discussion in relation to FIG. 14 of the external pump that is used to transport fluid to the sample inlet channel. Microvalve 72 has no relation to the external pump and merely functions as a valve to close the sample inlet channel 50. Therefore, although Quake discusses the use of microvalves 72 and 74 to form the closed loop 58, Quake provides no discussion related to a pump in communication with and operable to transport a sample solution through flow channels, where the first valve of the set of loop forming control valves comprises a control channel of the pump used to transport sample solution to the target loop.

On page 4 of the Final Office Action, the Examiner states that the "loop can be formed by actuating independently controlled elastomeric valves that can also act as a pump (see [0079])." Despite the reference to paragraph [0079] of Quake, there is no support in Quake for the Examiner's conclusory statement that microvalves 72 and 74 "act as a pump." On the contrary, the only use of microvalves 72 and 74 is to open and close the sample inlet and sample outlet channels.

The first portion of paragraph [0079] of Quake discusses the target loop being fed by a loop inlet and drained by a loop outlet. The remainder of paragraph [0079] merely discusses the peristaltic pump 78, which is internal to the closed loop. It appears that the Examiner, in attempting to find the claimed elements in Quake, has confused the claimed pump and recirculating pump, improperly using the internal peristaltic pump 78 of Quake to read on both the pump (external to the closed loop) and the recirculating pump recited in claim 14. This confusion results in the Examiner making several incorrect statements in the Final Office Action.

In responding to Applicant's arguments, the Examiner states on pages 6 and 7 of the Final Office Action that "Quake et al. disclose the use of independently actuated control channels that can be pressurized to form closed loop channels within its device, wherein the control channels can also be sequentially actuated to pump fluid through the closed loop channels (see [0079])." (Emphasis Added). As shown below, this statement by the Examiner is clearly wrong and demonstrates the Examiner's evident confusion.

As clearly shown in FIG. 14 of Quake, the peristaltic pump 78 is located ***inside*** the closed loop as appropriate for creating an internal pumping action inside the target loop 58.

The microvalves 72 and 74 that form target loop 58 are ***outside*** the closed loop and, therefore, cannot serve any function in pumping fluid through the closed loop using peristaltic pumping. Once microvalves 72 and 74 are actuated to form the closed loop, they cannot be used to pump fluid through the closed loop.

On page 7 of the Final Office Action the Examiner then concludes: "Quake et al. disclose the feature "wherein the first valve of the set of loop forming control valves comprises a control channel of the pump." Quake makes no such statement and Quake's disclosure provides no suggestion that would support this conclusory statement. Quake does not teach or suggest that microvalve 72 is a portion of an external pump used to transport fluid to target loop 58. As stated above, the sole purpose discussed by Quake for microvalve 72 is to open and close the sample inlet channel. Whether through confusion or mistake, and despite the Examiner's conclusory statement, the Examiner has failed to show how Quake teaches or suggests the claim elements in compliance with MPEP 2413.03.

Applicants suggest that because the Examiner found no support in Quake for a loop forming control valve that also serves as a control channel of a pump external to the closed loop, the Examiner has evidently used Quake's discussion of loop forming control valves and peristaltic pumping as a starting point for impermissible hindsight. MPEP 2142 is very clear that any suggestion to modify a reference must be found in the prior art, and cannot be based upon Applicants' own disclosure. Here, the Examiner appears to be using impermissible hindsight.

In conclusion, Quake does not teach or suggest the use of one of the control channels of a pump outside the closed loop as a valve to form the closed loop as recited by claim 14. Claim 34 recites elements similar to claim 14.

Claims 15, 18-20, 23-26, and 28-31 and 35-37, and 39-40, which depend from claims 14 and 34, respectively, are in condition for allowance, for at least the reasons discussed in relation to claims 14 and 34, as well as for the additional elements they recite. For at least these reasons, Applicants respectfully submit that the rejections of the claims are improper and should be overturned.

Claim 27

In the Final Office Action dated April 15, 2011, claim 27 was rejected under 35 U.S.C. § 103(a) as being unpatentable over Van Dam et al. in view of Quake et al. as applied

above and further in view of Raillard et al. (U.S. Patent Application Publication No. 2002/0102577). The Appellants respectfully traverse.

Claim 27, which depends from claim 23, is in condition for allowance, for at least the reasons discussed in relation to claim 23, as well as for the additional elements it recites.

8. CLAIMS APPENDIX

1. - 13. (Canceled).

14. (Previously Presented) A method of conducting a binding assay, comprising:

(a) providing a microfluidic device comprising a solid substrate layer having a surface that is capable of attaching ligand and/or anti-ligand, and an elastomeric layer attached to said solid substrate surface, wherein said elastomeric layer comprises:

(i) a plurality of first flow channels;

(ii) a plurality of second flow channels each intersecting and crossing each of the first flow channels thereby providing a plurality of intersecting areas formed at intersections between the first flow channels and the second flow channels, wherein the plurality of first flow channels and the plurality of second flow channels are adapted to allow the flow of a solution therethrough, wherein the solid substrate surface is in fluid communication with at least the intersecting areas of the plurality of first flow channels and the plurality of second flow channels, and wherein the plurality of first flow channels and/or the plurality of second flow channels are capable of forming a plurality of closed looped flow channels, wherein the plurality of second flow channels are in communication with a pump, and wherein a sample solution is transported through the plurality of second flow channels under the action of the pump, wherein the pump comprises more than one control channel each formed within the elastomeric layer and separated from the plurality of second flow channels by an elastomeric segment that is deflectable into the plurality of second flow channels in response to an actuation force, whereby the sample solution is transported along the plurality of second flow channels upon independent, sequential actuation of the more than one control channels;

(iii) a plurality of control channels;

(iv) a plurality of first control valves each operatively disposed with respect to each of the first flow channels to regulate flow of the solution through the first flow channels, wherein each of the first control valves comprises a first control channel and an elastomeric segment that is deflectable into or retractable from the first flow channel upon which the first control valve operates in response to an actuation force applied to the first control channel, the

elastomeric segment when positioned in the first flow channel restricting solution flow therethrough;

(v) a plurality of second control valves each operatively disposed with respect to each of the second flow channels to regulate flow of the solution through the second flow channels, wherein each of the second control valves comprises a second control channel and an elastomeric segment that is deflectable into or retractable from the second flow channel upon which the second control valve operates in response to an actuation force applied to the second control channel, the elastomeric segment when positioned in the second flow channel restricting solution flow therethrough;

(vi) a plurality of sets of closed loop forming control valves each set having a first valve operatively disposed with respect to an inlet of one of each of the first and/or the second flow channels and a second valve operatively disposed with respect to an outlet of one of each of the first and/or second flow channels to form the plurality of closed looped flow channels, wherein each of the loop forming control valves comprises a loop forming control channel and an elastomeric segment that is deflectable into or retractable from the first and/or the second flow channels upon which the loop forming control valve operates in response to an actuation force applied to the loop forming control channel, the elastomeric segment when positioned in the first and/or the second flow channels restricting solution flow therethrough thereby forming the looped flow channel, wherein the first valve of the set of loop forming control valves comprises a control channel of the pump that is independently actuated with respect to other control channels of the pump; and

(vii) a plurality of recirculating pumps, and wherein each recirculating pump is operatively disposed with respect to one of the closed looped flow channels such that circulation of solution through each of the closed looped flow channels can be regulated by one of the recirculating pumps;

(b) applying an actuating force to the second control valves to restrict solution flow through each of the second flow channels;

(c) introducing a reagent comprising a ligand into at least one of the first flow channels under conditions sufficient to attach the ligand to the solid substrate surface;

(d) removing the actuation force to the second flow channel control channel and applying an actuation force to the first control channel such that solution flow through the first flow channel is restricted; and

(e) performing a binding assay by introducing the sample solution into the second flow channel;

(f) applying an actuating force from two control lines to the plurality of sets of closed loop forming control valves to form the plurality of closed looped flow channels such that each closed looped flow channel comprises a closed loop spanning multiple rows and multiple columns; and recirculating the sample solution within the closed loop each of the closed looped flow channels using the recirculating pump under conditions sufficient to specifically bind an anti-ligand that may be present in the sample solution to the ligand that is attached to the solid substrate surface; and

(g) detecting the binding of the anti-ligand in the sample to the ligand.

15. (Original) The method of Claim 14 further comprising removing any ligand that is not attached to the solid substrate surface from the first flow channel prior to introducing the sample solution into the second flow channel.

16. - 17. (Canceled).

18. (Original) The method of Claim 14, wherein the plurality of first flow channels and the plurality of second flow channels are located within the elastomeric layer, and wherein each of the intersecting areas formed at intersections between the first flow channels and the second flow channels comprises a via which is in fluid communication with the solid substrate surface thereby forming a well that is adapted to collect a fluid therein.

19. (Original) The method of Claim 14, wherein the first flow channel is in communication with a pump, and wherein the reagent is transported through the first flow channel under the action of the pump.

20. (Original) The method of Claim 19, wherein the pump comprises more than one control channels each formed within the elastomeric layer and separated from the first flow channel by an elastomeric segment that is deflectable into the first flow channel in response to an actuation force, whereby the reagent is transported along the first flow channel.

21. - 22. (Canceled).

23. (Original) The method of Claim 14, wherein said step (e) of performing binding assay comprises removing the elastomeric layer from the solid substrate surface and determining ligand/antiligand binding at each of the intersecting areas with a detector.

24. (Original) The method of Claim 23, wherein the detector detects an optical signal within the intersecting areas.

25. (Original) The method of Claim 24, wherein the detector detects a fluorescence emission, fluorescence polarization or fluorescence resonance energy transfer.

26. (Original) The method of Claim 24, wherein the detector is an optical microscope, a confocal microscope or a laser scanning confocal microscope.

27. (Original) The method of Claim 23, wherein the detector is a non-optical sensor selected from the group consisting of a radioactivity sensor, and an electrical potential difference sensor.

28. (Previously Presented) The method of Claim 14, wherein the assay comprises detecting binding between a substrate and a cell receptor; a substrate and an enzyme; an antibody and an antigen; a nucleic acid and a nucleic acid binding protein; a protein and a protein; a small molecule and a protein; a small molecule and an oligonucleotide; or a protein affinity tag and a metal ion.

29. (Original) The method of Claim 14, wherein the assay is an assay for detecting a toxic effect on cells or a cell death assay, or a cell proliferation assay.

30. (Original) The method of Claim 14, wherein the assay is an oligonucleotide binding assay or a peptide binding assay.

31. (Previously Presented) The method of Claim 14, wherein the assay is an antimicrobial assay.

32. - 33. (Canceled).

34. (Previously Presented) A method of conducting a binding assay, comprising:

(a) providing a microfluidic device comprising a solid substrate layer having a surface that is capable of attaching ligand and/or anti-ligand, and an elastomeric layer attached to said solid substrate surface, wherein said elastomeric layer comprises:

(i) a first flow channel;

(ii) a second flow channel intersecting and crossing the first flow channel thereby providing an intersecting area formed at an intersection between the first flow channel and the second flow channel, wherein the first flow channel and the second flow channel are adapted to allow the flow of a solution therethrough, wherein the solid substrate surface is in fluid communication with at least the intersecting area of the first flow channel and the second flow channel, and wherein the first flow channel and/or the second flow channel are capable of forming a closed looped flow channel, wherein the second flow channel is in communication with a pump, and wherein a sample solution is transported through the second flow channel under the action of the pump, wherein the pump comprises more than one control channel each formed within the elastomeric layer and separated from the second flow channel by an elastomeric segment that is deflectable into the second flow channel in response to an actuation force, whereby the sample solution is transported along the second flow channel upon independent, sequential actuation of the more than one control channels;

(iii) a plurality of control channels;

(iv) a first control valve operatively disposed with respect to the first flow channel to regulate flow of the solution through the first flow channel, wherein the first control valve comprises a first control channel and an elastomeric segment that is deflectable into or retractable from the first flow channel upon which the first control valve operates in response to an actuation force applied to the first control channel, the elastomeric segment when positioned in the first flow channel restricting solution flow therethrough;

(v) a second control valve operatively disposed with respect to the second flow channel to regulate flow of the solution through the second flow channel, wherein the second control valve comprises a second control channel and an elastomeric segment that is deflectable into or retractable from the second flow channel upon which the second control valve operates in response to an actuation force applied to the second control channel, the elastomeric segment when positioned in the second flow channel restricting solution flow therethrough;

(vi) a first loop forming control valve operatively disposed with respect to an inlet of one of the first and/or the second flow channels and a second loop forming control valve

operatively disposed with respect to an outlet of one of the first and/or second flow channels to form the closed looped flow channel, wherein each of the first and second loop forming control valves comprises a loop forming control channel and an elastomeric segment that is deflectable into or retractable from the first and/or the second flow channels upon which the loop forming control valve operates in response to an actuation force applied to the loop forming control channel, the elastomeric segment when positioned in the first and/or the second flow channels restricting solution flow therethrough thereby forming the closed looped flow channel, wherein the first loop forming control valve comprises a control channel of the pump that is independently actuated with respect to other control channels of the pump; and

(vii) a recirculating pump operatively disposed with respect to the closed looped flow channel such that circulation of solution through the closed looped flow channel can be regulated by the recirculating pump;

(b) applying an actuating force to the second control valve to restrict solution flow through the second flow channel;

(c) introducing a reagent comprising a ligand into the first flow channel under conditions sufficient to attach the ligand to the solid substrate surface;

(d) removing the actuation force to the second flow channel control channel and applying an actuation force to the first control channel such that solution flow through the first flow channel is restricted; and

(e) performing a binding assay by introducing a sample solution into the second flow channel;

(f) applying an actuating force to the first loop forming control valve using a first control line and to the second loop forming control valve using a second control line to form the closed looped flow channel such that the closed looped flow channel comprises a closed loop; and recirculating the sample solution within the closed loop of the closed looped flow channel using the recirculating pump under conditions sufficient to specifically bind an anti-ligand that may be present in the sample solution to the ligand that is attached to the solid substrate surface; and

(g) detecting the binding of the anti-ligand in the sample to the ligand.

35. (Previously Presented) The method of Claim 34, wherein the first flow channel and the second flow channel are located within the elastomeric layer, and wherein the

intersecting area formed at the intersection between the first flow channel and the second flow channel comprises a via which is in fluid communication with the solid substrate surface thereby forming a well that is adapted to collect a fluid therein.

36. (Previously Presented) The method of Claim 34, wherein said step (e) of performing binding assay comprises removing the elastomeric layer from the solid substrate surface and determining ligand/antiligand binding at the intersecting area with a detector, wherein the detector detects an optical signal within the intersecting areas, and wherein the detector detects a fluorescence emission, fluorescence polarization, or fluorescence resonance energy transfer.

37. (Previously Presented) The method of Claim 34, wherein said step (e) of performing binding assay comprises removing the elastomeric layer from the solid substrate surface and determining ligand/antiligand binding at the intersecting area with a detector, wherein the detector detects an optical signal within the intersecting areas, and wherein the detector is an optical microscope, a confocal microscope, or a laser scanning confocal microscope.

38. (Canceled).

39. (Previously Presented) The method of Claim 34, wherein the second flow channel is in communication with a pump comprising a plurality of sequentially actuated control channels, and wherein the sample solution is transported through the second flow channel under the action of the pump.

40. (Previously Presented) The method of Claim 39, wherein the first loop forming control valve comprises a control channel of the pump.

9. EVIDENCE APPENDIX

None.

10. RELATED PROCEEDINGS APPENDIX

None.

CONCLUSION

For at least the reasons discussed in Section 7, it is respectfully submitted that the rejection should be reversed.

Respectfully submitted,

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